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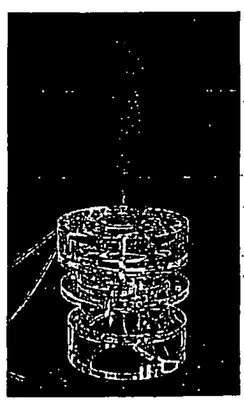
(54) Title: ULTRASOUND DRIVEN DEVICE FOR ACCELERATED TRANSFER OF SUBSTANCES ACROSS POROUS BOUNDARIES



(57) Abstract: Apparatus is described which utilises megahertz ultrasound from a concave piezoelectric transducer to produce liquid jets which penetrate into or through porous media such as human or animal skin and egg shells. The invention permits high power ultrasound to be decoupled from the skin or shell avoiding undesirable temperature rise or other bioeffects of ultrasound. The liquid can be water or a drug or anaesthetic. By pulsing the electrical drive signal the apparatus can be utilised to produce liquid droplets with a predetermined size distribution suited to drug delivery by inhalation. A device in the form of a gun has been devised into which cartons of drug, vaccine or other liquid material can be plugged so that repeated use of the device is made possible. The droplet formation can also be performed in a cylindrical form of apparatus and the cloud of drops can be driven towards or into the nose or mouth of a patient using a suitable fan and pipework. The requirement of both types of device is that an ultrasonic focus coincides within a few millimetres above or below the liquid level from which drug delivery is required. The same condition applies where controlled droplet formation is the objective.

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ULTRASOUND DRIVEN DEVICE FOR ACCELERATED TRANSFER OF SUBSTANCES ACROSS POROUS BOUNDARIES

FIELD OF THE INVENTION

The present invention relates to an apparatus and a method for using ultrasound to produce liquid jets which penetrate into or through porous media.

BACKGROUND OF THE INVENTION

There is considerable interest in delivering drugs and vaccines transdermally without the use of a hypodermic needle and syringe. There are two methods currently employed: one uses compressed helium gas to drive powdered preparations through the epidermis at high speed and the other uses compressed nitrogen gas to 'squirt' liquid formulations of drugs at the epidermis. This type of device has a limited supply of gas and is normally disposable after one or two uses. This increases significantly the cost of drug delivery. In consequence there is enormous interest in an electronically driven system which can facilitate rapid delivery of drugs and be capable of being used and re-used indefinitely.

WO 00/21605 discloses a method and an apparatus for delivering active agents across or into a porous surface by ultrasound phonophersis in which an ultrasound beam is focussed on the porous surface.

SUMMARY OF THE INVENTION

According to a first aspect of the present invention there is provided an apparatus for phonophoretic transfer of a liquid into or through a porous medium, said apparatus comprising: a housing; a first chamber in the housing for holding a liquid said chamber having an opening in a side thereof; an ultrasound transducer mounted in the housing for generating a sound beam; a focussing device for focusing the sound beam to a focus; said ultrasound transducer having an operating frequency between 0.5 and 5 MHz and said focus being located within the first chamber, whereby in use the focus is located at an air/liquid interface for generating a jet of liquid which projects through the opening.

Preferably, the ultrasound transducer and the focussing device are integral forming a focussed ultrasound transducer.

Preferably, the transducer is air-backed.

Preferably, the apparatus further comprises an ultrasound power generator for driving said transducer.

Preferably, the apparatus further comprises a pistol grip having a trigger which activates the device.

Preferably, the apparatus further comprises an acoustic reflector.

Preferably, the acoustic reflector is a metal plate.

Preferably, the acoustic reflector is a stainless steel plate.

Preferably, the acoustic reflector is air-backed.

Preferably, the acoustic reflector is inclined at between 10 and 45 degrees to the horizontal.

Preferably, the apparatus further comprises a second chamber.

Preferably, the apparatus further comprises a membrane, said membrane separating the first chamber and the second chamber.

Preferably, said membrane is impervious to the transfer of air or dissolved gases.

Preferably, the housing comprises two parts which are held together and sealed.

Preferably, the membrane is located between the two parts of the housing.

Preferably, the transducer is sealed to the housing forming a third chamber at a rear side of said transducer.

Preferably, the operating frequency of the transducer is 2 MHz.

Preferably, the transducer is arranged to generate a continuous sound wave beam.

Alternatively, the transducer is arranged to generate a sound beam which is pulsed on and off.

Preferably, the transducer is arranged to generate a pulsed sound beam which is pulsed on for 10 millisecond and off for 50 millisecond.

According to a second aspect of the present invention there is provided a method of phonophoretic transfer of a liquid into or through a porous medium, which method comprises: providing a body of liquid held in a first chamber whereby the body of liquid has a liquid / air interface; generating a sound beam having a frequency between 0.5 and 5 MHz; focusing the sound beam on the liquid / air interface thereby generating a jet of the liquid which projects from the interface, said jet of liquid impinging on the porous medium whereby a portion of the liquid is transferred into or through the porous medium.

Preferably, the liquid in the jet which is not transferred into or through the porous medium falls back into the first chamber thereby recycling said liquid which is not transferred.

Preferably, the liquid is selected from one of a drug, a vaccine, an anaesthetic, a paint and a toxic material.

Preferably, a body of non-cavitating liquid is provided in a second chamber.

Preferably, the non-cavitating liquid is distilled degassed water.

According to a third aspect of the present invention there is provided a method of generating a jet of liquid, which method comprises: providing a body of liquid held in a first chamber whereby the body of liquid has a surface; generating a sound beam having a frequency between 0.5 and 5 MHz; focusing the sound beam on the surface of the liquid thereby generating a jet of the liquid which projects from the surface.

Preferably, the jet comprises droplets and a fan is provided which transports the droplets within the jet.

BRIEF DESCRIPTION OF THE DRAWINGS

Embodiments of the present invention will now be described by way of example with reference to the accompanying drawings in which:

Figure 1 shows an apparatus for demonstrating the effect of focussing ultrasound on a liquid / air interface in accordance with the invention;

Figure 2 is a vertical section showing schematically a device for transdermally delivering substances by ultrasound but avoiding sonification of the skin in accordance with an embodiment of the invention;

Figure 3 is a vertical section showing schematically the device shown in Figure 2 in use;

Figure 4 is a plan view of the device shown in Figure 2, omitting pistol grip to improve clarity;

Figure 5 shows an ultrasonic power generator for use with the device of Figure 2;

Figure 6 shows a circuit diagram of an oscillator employed in the power generator shown in Figure 5;

Figure 7 is a circuit diagram of a power amplifier where the input is generated by the oscillator described in Figure 6; and

Figure 8 shows pulse circuitry to control output from the power amplifier of Figure 7.

DESCRIPTION OF THE PREFERRED EMBODIMENT

In devising the present invention, the inventors investigated the effect of focussing ultrasound on a liquid / air interface and produced the apparatus shown in Figure 1 for demonstrating such effects. Figure 1 shows an apparatus comprising a chamber holding a liquid and a circular focussed ultrasound transducer for generating a sound beam which is connected via a cable to an ultrasonic power generator (not shown). Two tubes are connected to the chamber for filling and emptying the chamber so as to maintain the liquid / air interface at the focus of the transducer. The transducer has an operating frequency between 0.5 and 5 MHz and has a focus which coincides with an upper surface of the liquid in the chamber at the liquid / air interface. The operating frequency was 2 MHz, the acoustic power was circa 40 Watts and the output was pulsed 75 milliseconds on and 150 milliseconds off. In the course of investigating the effects of a beam of focussed ultrasound propagating through a liquid, the inventors observed that when the focus coincides with a liquid / air interface as in figure 1 that streams of liquid droplets are projected upwards at high speed reaching considerable height. Even when the ultrasound is limited to a 10 milli-second pulse it was still possible to observe the effect. Jets composed of droplets rose far above the water surface for a range of ultrasound pulses of varying length and various values of off times (e.g. 10 milli-seconds on 20 milliseconds off).

The effect (i.e. of a large number of individual trajectories emerging from the liquid phase into air) only became apparent when recorded photographically using a slow film speed, e.g. 50 ASA Fujichrome Velvia film.

Without being bound by theory, as the inventors presently understand the mechanism of jet formation, gaseous cavitation causes the occurence of an unexpectedly high value of ultrasonic absorption coefficient, μ, and consequent large pressure gradient $\Delta P / \Delta x$ in the

fluid near the ultrasonic focus. This violent fluid streaming, along the axis of the beam, can itself propel the liquid upwards into the air. Also there seems to be another enhancing effect namely the small gaseous cavities induced by the sound wave merge into a single larger cavity which collapses producing a shock wave which adds kinetic energy to the upward motion of the fluid. The relative importance of these two effects is presently unclear. One can hear audible sounds associated with violent collapse of cavities.

Theory indicates, in a plane sound beam produced by a circular piston transducer vibrating in its thickness mode, that the driving pressure ΔP is given by

$\Delta P = I / c \, [\exp(-\mu x_1) - \exp(-\mu x_2)]$ where I is intensity, c is the velocity of sound, μ is the absorption coefficient and x_1 and x_2 are the chosen distances along the beam axis. For a focussed beam and with cavitation occuring, no equivalent theory, as far as we are aware, has been developed . The driving pressure ΔP clearly leads to fluid streaming but the magnitude depends on the absorption coefficient (in the present case anomolously high due to cavitation).

The significance of these observations is that it is possible to use ultrasound to drive fluids towards the skin at high speed without the ultrasound beam being directly incident upon and reaching the skin. Clearly avoiding ultrasonic treatment of the skin avoids any possibility of heating or other undesirable bioeffects on skin or underlying tissues.

To utilise the effect to deliver drugs or vaccines in fluid formulation it is necessary to devise an arrangement so that a liquid / air interface is situated within a suitably sized compartment adjacent to the skin. Preferably, the ultrasound beam is propagated into that compartment without significant attenuation. Accordingly, distilled degassed water, which has a very small attenuation coefficient, may be situated on the side next to the drug compartment. Since it is preferable for the drug not to be diluted (or the dose would not be controlled) an airtight membrane, transparent to ultrasound, may be provided in order to separate the two compartments.

In order to maintain an upward flow of liquid, in jet or droplet form, the sound beam is directed (in the simplest case) vertically upwards. In consequence a 45 degree reflector is located in the drug compartment and the focus of the beam coincides with the level of the

liquid containing the drug to be delivered. In this way a fountain-like stream of fluid strikes the skin and part of it is absorbed through the pores and hair follicles. The part not absorbed drops back into the cup and is recycled until all the dose is delivered.

A suitable arrangement for transdermal drug delivery is shown in vertical section in Figure 2. The device comprises a transducer 1, a housing 40, a first chamber 30, a second chamber 6, a third chamber 50, an acoustically transparent membrane 4 separating the first and second chambers, a reflector plate 3, a pistol grip 8 having a trigger 7, and a BNC connector 9. The two chambers / compartments are held together and sealed by bolts 5. The ultrasonic transducer 1 is sealed to the housing and is air-backed for maximum power output. The reflector 3 may be a stainless steel plate or other metal plate air-backed to provide good acoustically reflective properties. The device can be housed inside an outer casing to improve its aesthetic appeal. The membrane 4 can be positioned beyond the reflector plate if this proves more convenient for manufacture of the device.

Figure 3 shows the device of Figure 2 in use. The transducer 1 directs a beam of sound from a first chamber through the acoustically transparent membrane 4 into the second chamber containing an aqueous formulation of drug or vaccine. The reflector plate directs the ultrasound vertically upward and the geometry is chosen so that the focus lies at the liquid / air interface. The walls of the drug containing chamber are chosen so that the upward jets described in Figure 1 strike any surface placed at 2. The skin would normally be located at 2. The pistol grip 8 has a trigger 7 which switches on the ultrasonic excitation from a generator connected to a BNC connector 9. The compartments housing the drug and the transducer are held together and sealed by bolts 5. The ultrasonic transducer 1 is sealed to the housing and is air-backed for maximum power output. Jets and droplets emerge within the drug compartment and the direction is indicated by arrows. The reflector 3 may be a stainless steel plate or other metal plate air-backed to provide good acoustically reflective properties. The vertical orientation of the drug compartment could be modified to lie at an acute angle provided only that the liquid / air interface is maintained. The device can be housed inside an outer casing to improve its aesthetic appeal. The drug could be introduced in a small thin walled tub. The membrane 4 can be positioned beyond the reflector plate if this proves more convenient for manufacture of the device.

A plan view of the drug delivery gun is shown schematically in Figure 4. The compartment on the left containing the transducer 10 contains distilled degassed water (or other fluid with near zero ultrasonic absorption coefficient). This chamber carries the ultrasound into the drug containing compartment 12 on the right. The sound is reflected by the plate 11 and the beam comes to a focus at the liquid surface. The volume behind the transducer is occupied by air. The electrical connections to the transducer faces and to the BNC connector are omitted to avoid confusion.

The two chambers are separated by a thin acoustically transparent membrane which is diffusion proof to gas passing (backwards) from the drug compartment into the degassed water. The pistol grip and trigger are also omitted for the sake of clarity as are wiring connections.

The device, called a phonophoretic gun, is placed against the skin (or other porous surface) and the sound switched on either in continuous or pulsed mode. The jets and streams of droplets, containing the drug or vaccine, strike the skin and a percentage is transferred into subcutaneous layers. The fraction not taken up by the target falls back into the drug compartment (indicated by arrows in Figure 2) and is recycled until the desired dose is delivered.

Accordingly, the jet impinges on the skin 2 and liquid not transferred into the porous material in one pulse of the ultrasound falls back to be recycled in the next. The output of a pulsed ultrasound power generator shown in Figure 5 and whose circuitry is described in Figures 6, 7 and 8 drives the piezoelectric transducer which leads to jet formation.

The ultrasound power generator used in this embodiment gives out up to 50 Watts of acoustic power at frequencies of 2MHz, 1 MHz and 250 kHz. An LCD meter reads in percent of maximum output. The sound intensity at the focus can reach in excess of 100 Watts per cm^2. It operates in pulsed mode down to a single pulse of 10 milliseconds duration (on time) and a wide range of off times and can be run for total times up to 90 minutes in automatic mode. The objective however is to deliver useful drug doses in times from a few milliseconds to seconds.

Figure 5 shows the ultrasonic power generator which can operate at 3 frequencies: 2 MHz; 1 MHz; and 250 KHz, with variable pulse on and off times and variable total time. This generator drives the focussed transducer in the ultrasonic drug delivery gun. The power supply for the generator is selected from one of mains electricity and a rechargable battery.

Figure 6 is the circuit diagram of the 2 MHz oscillator we have employed in the power generator of Figure 5. The oscillators for other frequencies are of similar design but with different component values. The 2 MHz signal is fed to a power amplifier.

Figure 7 is the circuit diagram of the power amplifier where the input is generated by the oscillator described in Figure 6. The power amplifier generates the signal to excite the ultrasound piezoelectric bowl shaped transducers.

Figure 8 is the pulse circuitry used to control the output from the power oscillator and thus to provide the pulsed output which excites the ultrasound focussed bowls used to produce the liquid jets and droplets employed for drug / vaccine delivery. The pulse circuitry controls output from the power amplifier allowing excitation by continuous or a wide range of pulsing regimes. That is, on times and off times of the ultrasound beam can be chosen from a wide range of values.

Other embodiments of the invention are envisaged. The material forming the jet and droplets may be chosen to overcome an assailant by projecting a toxic or anaesthetic spray towards the face. Alternatively, an embodiment may be provided for use in a respirator/inhaler, which may include a fan and tubes, whereby droplets of fluid are transported by the fan or other means along the tubes to the face for inhalation.

CLAIMS

1. An apparatus for phonophoretic transfer of a liquid into or through a porous medium, said apparatus comprising:

a housing;

a first chamber in the housing for holding a liquid said first chamber having an opening in a side thereof;

an ultrasound transducer mounted in the housing for generating a sound beam;

a focussing device for focusing the sound beam to a focus;

said ultrasound transducer having an operating frequency between 0.5 and 5 MHz and said focus being located within the first chamber,

whereby in use the focus is located at an air / liquid interface for generating a jet of liquid which projects through the opening.

2. An apparatus according to claim 1, wherein the ultrasound transducer and the focussing device are integral forming a focussed ultrasound transducer.

3. An apparatus according to claim 1 or claim 2, wherein the transducer is air-backed.

4. An apparatus according to any preceding claim, wherein the apparatus further comprises an ultrasound power generator for driving said transducer.

5. An apparatus according to any preceding claim, wherein the apparatus further comprises a pistol grip having a trigger which activates the device.

6. An apparatus according to any one of the preceding claims, wherein the apparatus further comprises an acoustic reflector.

7. An apparatus according to claim 6, wherein the acoustic reflector is a metal plate.

8. An apparatus according to claim 6 or claim 7, wherein the acoustic reflector is a stainless steel plate.

9. An apparatus according to any one of claims 6 to 8, wherein the acoustic reflector is air-backed.

10. An apparatus according to any one of claims 6 to 9, wherein the acoustic reflector is inclined at between 10 and 45 degrees to the horizontal.

11. An apparatus according to any previous claim, wherein the apparatus further comprises a second chamber.

12. An apparatus according to claim 11, wherein the apparatus further comprises a membrane, said membrane separating the first chamber and the second chamber.

13. An apparatus according to claim 12, wherein said membrane is impervious to the transfer of air or dissolved gases.

14. An apparatus according to any preceding claim, wherein the housing comprises two parts which are held together and sealed.

15. An apparatus according to claim 14 when appended to claim 12 or claim 13, wherein the membrane is located between the two parts of the housing.

16. An apparatus according any previous claim, wherein the transducer is sealed to the housing forming a third chamber at a rear side of said transducer.

17. An apparatus according to any previous claim, wherein the first chamber has an opening in an upper side thereof.

18. An apparatus according to any one of the preceding claims, wherein the operating frequency of the transducer is 2 MHz.

19. An apparatus according to any one of the preceding claims, wherein the transducer is arranged to generate a continuous sound wave beam.

20. An apparatus according to any one of the preceding claims, wherein the transducer is arranged to generate a sound beam which is pulsed on and off.

21. An apparatus according to claim 20, wherein transducer is arranged to generate a pulsed sound beam which is pulsed on for 10 millisecond and off for 50 millisecond.

22. A method of phonophoretic transfer of a liquid into or through a porous medium, which method comprises:

providing a body of liquid held in a first chamber whereby the body of liquid has a liquid / air interface;

generating a sound beam having a frequency between 0.5 and 5 MHz;

focusing the sound beam on the liquid / air interface thereby generating a jet of the liquid which projects from the interface, said jet of liquid impinging on the porous medium whereby a portion of the liquid is transferred into or through the porous medium.

23. A method according to claim 22, wherein the liquid in the jet which is not transferred into or through the porous medium falls back into the first chamber thereby recycling said liquid which is not transferred.

24. A method according to claim 22 or claim 23, wherein the liquid is selected from one of a drug, a vaccine, an anaesthetic, a paint and a toxic material.

25. A method according to any one of claims 22 to 24, wherein the sound beam is generated by an ultrasound transducer.

26. A method according to claim 25, wherein the sound beam is focussed by the ultrasound transducer.

27. A method according to claim 25 or claim 26, wherein the transducer is air-backed.

28. A method according to any one of claim 25 to 27, wherein the transducer is driven by an ultrasound power generator.

29. A method according to any one of claims 25 to 28, wherein the transducer is activated by a trigger on a pistol grip.

30. A method according to any one of claims 22 to 29, wherein the sound beam is reflected by an acoustic reflector.

31. A method according to claim 30, wherein the acoustic reflector is a metal plate.

32. A method according to claim 30 or claim 31, wherein the acoustic reflector is a stainless steel plate.

33. A method according to any one of claims 30 to 32, wherein the acoustic reflector is air-backed.

34. A method according to any one of claims 30 to 33, wherein the acoustic reflector is inclined at between 10 and 45 degrees to the horizontal.

35 A method according to any one of claims 22 to 34, wherein a body of non-cavitating liquid is provided in a second chamber.

36. A method according to claim 35, wherein the non-cavitating liquid is distilled degassed water.

37. A method according to claim 35 or 36, wherein a membrane is provided which separates the first and second chambers.

38. A method according to claim 37, wherein said membrane is impervious to the transfer of air or dissolved gases.

39. A method according to claims 37 or 38, wherein a housing is provided comprising two parts which are held together and sealed with the membrane located therebetween.

40. A method according to claim 25, wherein the transducer is sealed to a housing forming a third chamber at a rear side of the transducer.

41. A method according to any one of claims 22 to 40, wherein the first chamber is vertically orientated with an opening in an upper side thereof whereby the jet of liquid projects through the opening.

42. A method according to claim 25, wherein the operating frequency of the transducer is 2 MHz.

43. A method according to claim 25, wherein the transducer is arranged to generate a continuous sound wave beam.

44. A method according to claim 25, wherein the transducer is arranged to generate a sound beam which is pulsed on and off.

45. A method according to claim 44, wherein the transducer is arranged to generate a pulsed sound beam which is pulsed on for 10 millisecond and off for 50 millisecond.

46. A method of generating a jet of liquid, which method comprises:

providing a body of liquid held in a first chamber whereby the body of liquid has a surface;

generating a sound beam having a frequency between 0.5 and 5 MHz;

focusing the sound beam on the surface of the liquid thereby generating a jet of the liquid which projects from the surface.

47. A method according to claim 46, wherein the jet comprises droplets and wherein a fan is provided which transports the droplets within the jet.

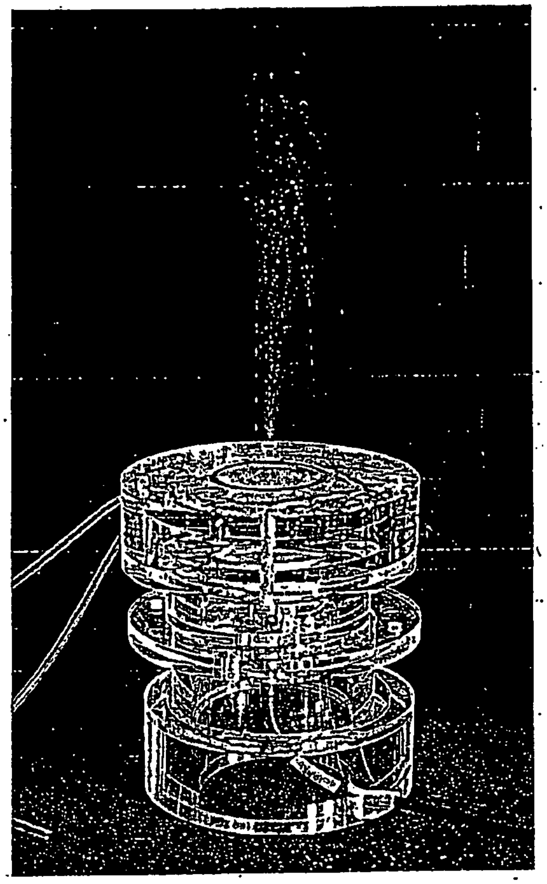


Figure 1

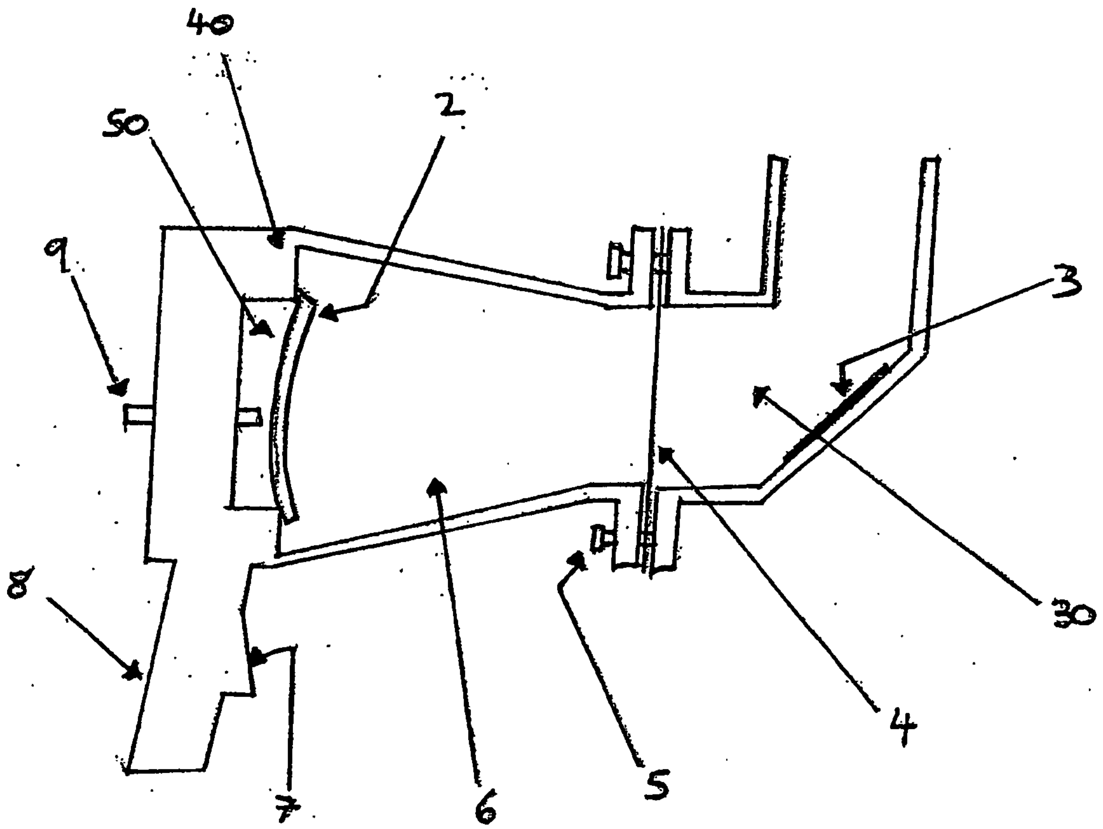


Figure 2

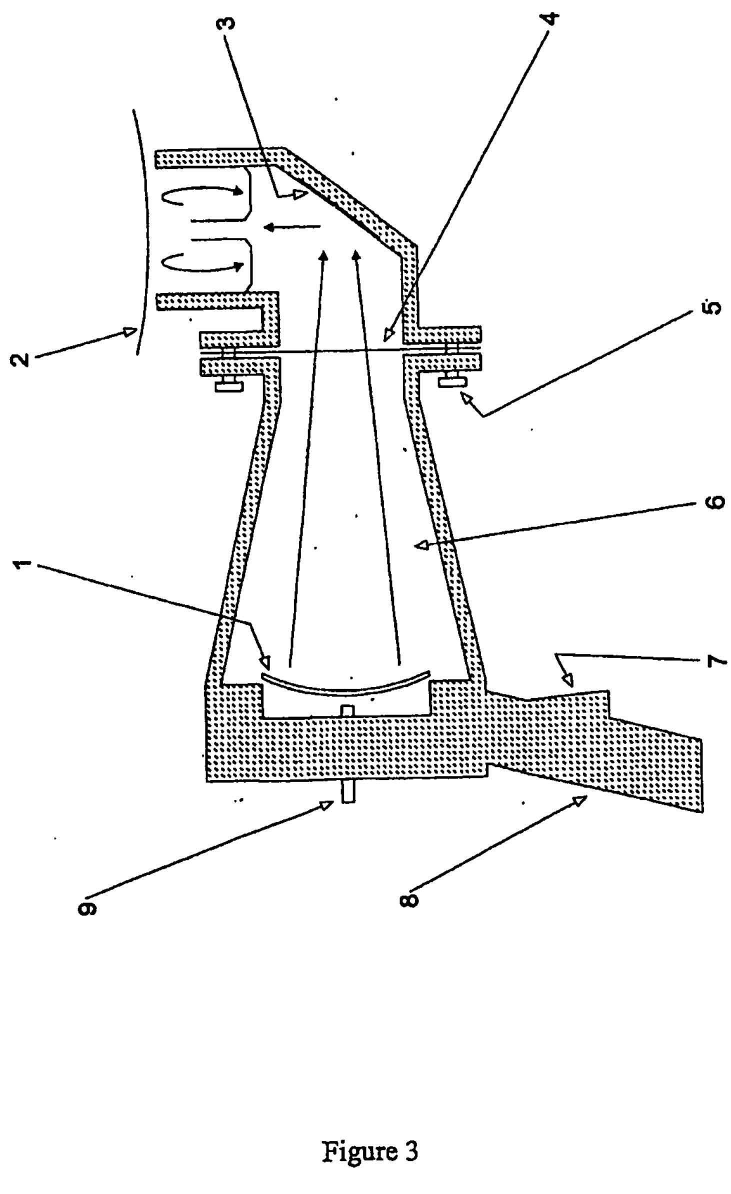


Figure 3

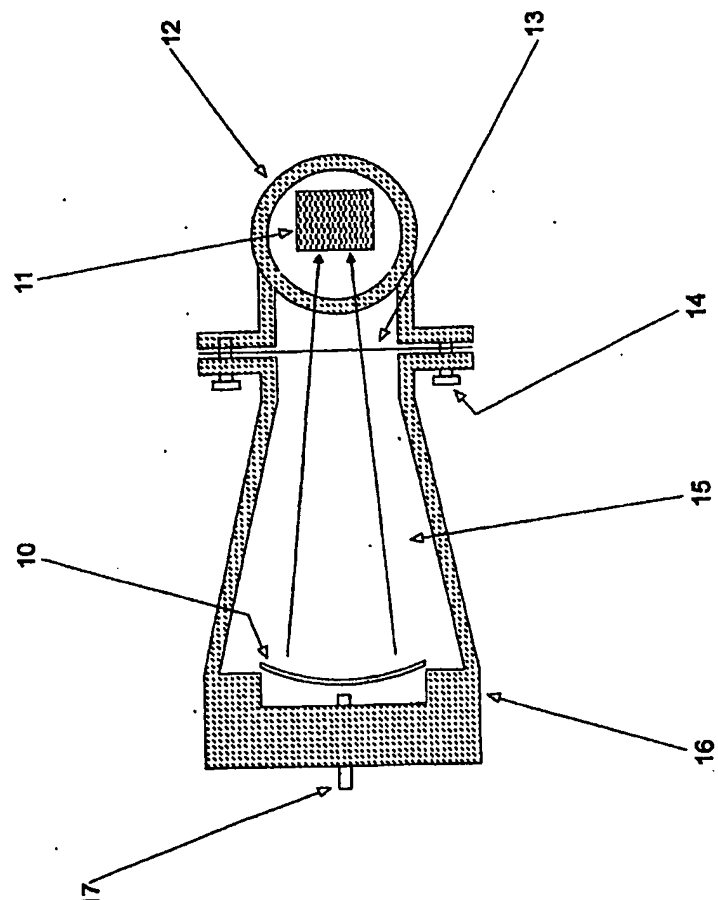


Figure 4

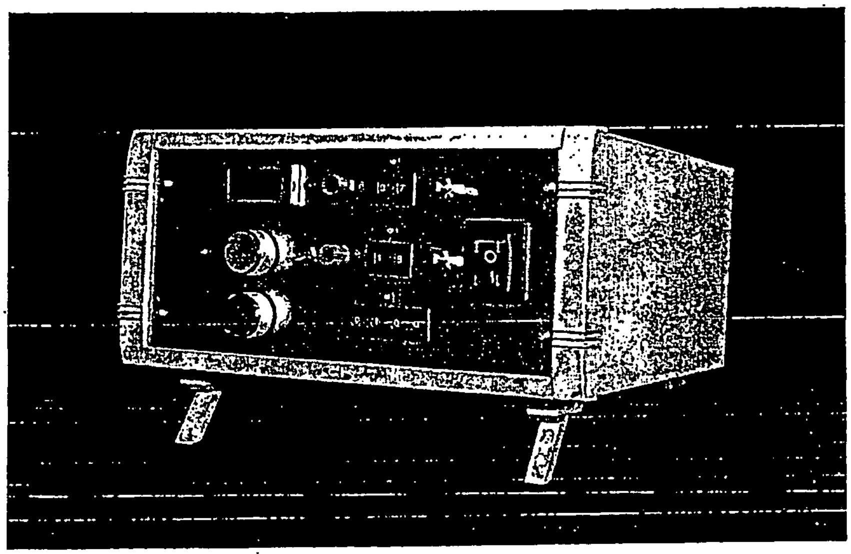
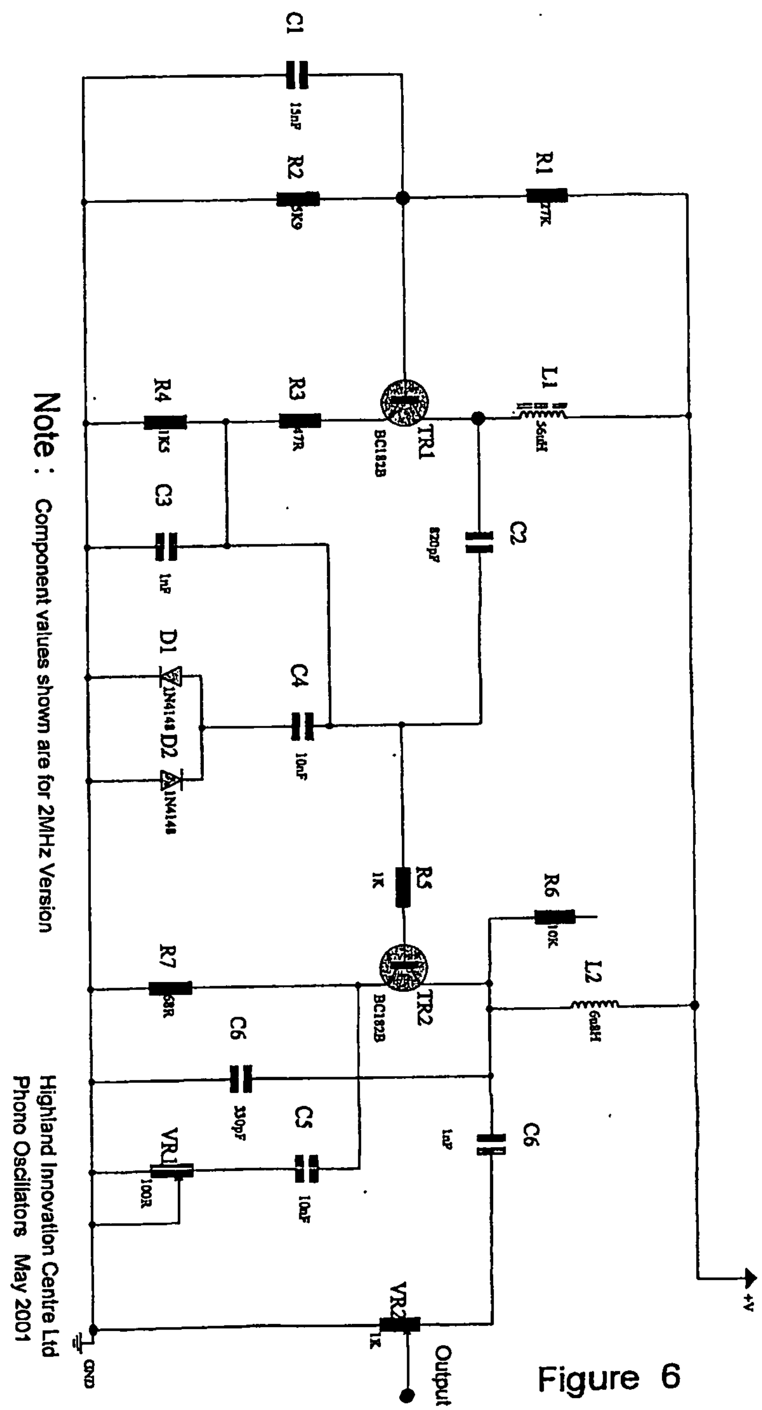


Figure 5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R2
3K9
R1
27K
L1
56uH
TR1
BC182B
R3
47R
R4
1K5
C3
1nF
C2
820pF
D1
1N4148
D2
1N4148
C4
10nF
R5
1K
R6
10K
L2
6uH
TR2
BC182B
R7
68R
C6
330pF
C5
10nF
VR1
100R
C6
1nF
VR2
1K
Output
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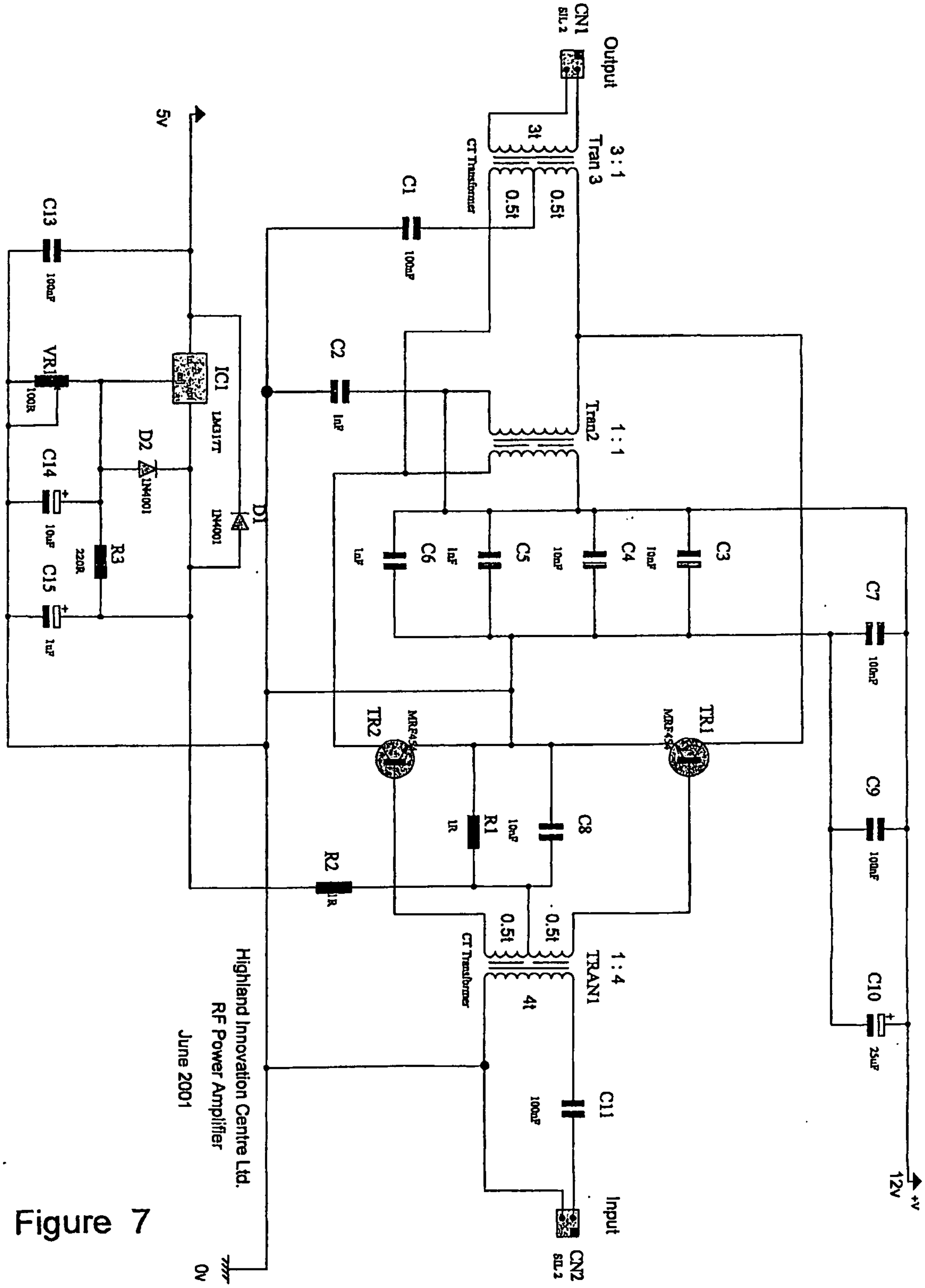
+V
Note : Component values shown are for 2MHz Version
Highland Innovation Centre Ltd
Phono Oscillators May 2001

Figure 6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SIL 2
Output
Tran 3
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3t
0.5t
0.5t
CT Transformer
C1
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5v
C13
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C2
1nF
IC1
LM317T
VR1
100R
Tran2
1 : 1
D2
1N4001
D1
1N4001
C14
10uF
R3
220R
C15
1uF
C6
1nF
C5
1nF
C4
10nF
C3
10nF
C7
100nF
TR2
MRF454
TR1
MRF454
R1
1R
C8
10nF
C9
100nF
R2
1R
0.5t
0.5t
CT Transformer
TRAN1
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C10
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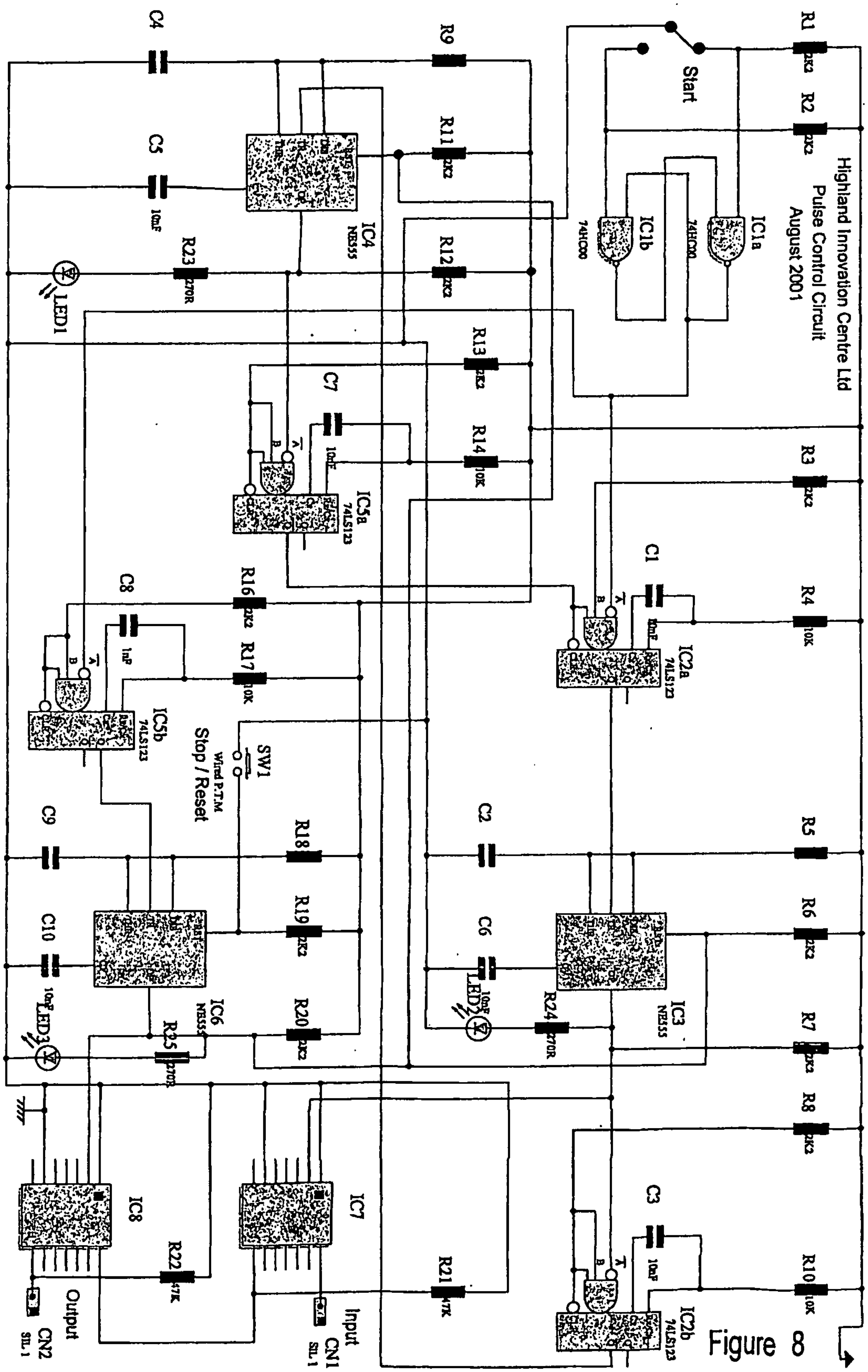
Highland Innovation Centre Ltd.
RF Power Amplifier
June 2001

Figure 7


Highland Innovation Centre Ltd
Pulse Control Circuit
August 2001
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IC1b
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IC2a
IC2b
74LS123
IC3
NE555
IC4
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IC5a
IC5b
74LS123
IC6
NE555
IC7
IC8
SW1
Wired P.T.M
Stop / Reset
LED1
LED2
LED3
Input
CN1
Output
CN2
SIL 1
R1
R2
R3
R4
R5
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R7
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R9
R10
R11
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R21
R22
R23
R24
R25
C1
C2
C3
C4
C5
C6
C7
C8
C9
C10

Figure 8